General

Guideline Title

Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline.

Bibliographic Source(s)

Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril. 2016 Dec;106(7):1634-47. [113 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the level of the evidence (Level I-III) and strength of the recommendations (Grade A-C) are given at the end of the "Major Recommendations" field.

Who Is at High Risk for Moderate and Severe Ovarian Hyperstimulation Syndrome (OHSS)?

Summary Statements

> There is fair evidence (level II-2) that polycystic ovary syndrome (PCOS), elevated antimüllerian hormone (AMH) values, peak estradiol levels, multifollicular development, and a high number of oocytes retrieved are associated with an increased risk of OHSS. (Grade B)
> While cut points require validation, AMH values >3.4 ng/mL, antral follicle count (AFC) >24, development of ≥25 follicles, estradiol values >3,500 pg/mL, or ≥24 oocytes retrieved are particularly associated with an increased risk of OHSS. (Grade B)

Prevention of OHSS

Does the Type of Stimulation Protocol Influence the Risk of OHSS?

Summary Statements

> There is good evidence to support the use of ovarian stimulation protocols using gonadotropin-

releasing hormone (GnRH) antagonists in order to reduce the risk of OHSS. (Grade A)
There is insufficient evidence that clomiphene independently reduces OHSS risk. (Grade C)

Can Aspirin Reduce the Risk of OHSS?

Summary Statement

There is fair evidence that aspirin reduces the incidence of OHSS based on a single randomized trial comparing aspirin alone with no treatment and another study comparing combined acetylsalicylic acid and steroid treatment with no treatment. (Grade B)

Can Metformin Reduce the Risk of OHSS?

Summary Statement

There is good evidence that metformin decreases the risk of OHSS risk in PCOS patients. (Grade A)

Can Coasting Reduce the Risk of OHSS?

Summary Statement

There is insufficient evidence to recommend coasting for the prevention of OHSS. (Grade C)

Choice of Trigger for Final Oocyte Maturation Prior to Retrieval

Summary Statements

There is insufficient evidence to recommend a lower dose of human chorionic gonadotropin (hCG) to trigger oocyte maturation for reduction in OHSS risk based on one underpowered randomized trial. (Grade C)
There is good evidence to recommend the use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval in order to reduce the risk of OHSS. (Grade A)
There is good evidence that live-birth rates are lower in fresh autologous cycles after GnRH trigger, but not donor-recipient cycles. (Grade A)
There is fair evidence that reproductive outcomes are improved when a low dose of hCG is co-administered at the time of GnRH agonist trigger for luteal support. (Grade B)

Dopamine Agonist

Summary Statement

There is good evidence that dopamine agonist administration starting at the time of hCG trigger for several days reduces the incidence of OHSS. (Grade A)

Can Albumin Prevent OHSS Risk?

Summary Statement

Given mixed results in the literature, there is insufficient evidence to conclusively state that albumin lowers the risk of OHSS. (Grade C)

Can Calcium Prevent OHSS Risk?

Summary Statement

There is fair evidence that calcium lowers OHSS risk. (Grade B)

Can Cryopreservation Prevent OHSS Risk?

Summary Statement

Based on the results of two small randomized controlled trials (RCTs), there is fair evidence that cryopreservation prevents OHSS. (Grade B)

Can Miscellaneous Treatments Prevent OHSS Risk?

There are insufficient data to make recommendations regarding the use of luteal antagonist administration, letrozole, methylprednisolone, intramuscular progesterone, or ketoconazole to mitigate OHSS risk.

Treatment of OHSS

Does Outpatient Paracentesis of Women with OHSS Improve Their Outcome?

Summary Statement

There is fair evidence to recommend paracenteses or culdocenteses for the management of OHSS in an outpatient setting. (Grade B)

Do Volume Expanders Improve Outcome for Women with OHSS?

Summary Statement

There is insufficient evidence to support the use of volume expanders alone for the treatment of OHSS (Grade C). The studies reporting use of volume expanders in OHSS treatment have not been uniform in treatment protocols. Some use diuretics and others include dopamine.

Recommendations

- Women with PCOS, elevated AMH values, and elevated AFC may benefit from ovarian stimulation protocols that reduce the risk of OHSS. (Grade B)
- Ovarian stimulation protocols using GnRH antagonists are preferable in women at high risk of OHSS. (Grade A)
- The use of a GnRH agonist to trigger oocyte maturation prior to oocyte retrieval is recommended to reduce the risk of OHSS if peak estradiol levels are high or multifollicular development occurs during stimulation. (Grade A) Low-dose hCG co-trigger, luteal hormonal support, or cryopreservation of embryos are strategies that may improve pregnancy rates in this setting. (Grade B)
- Dopamine agonist administration starting at the time of hCG trigger for several days also may be used to reduce the incidence of OHSS. (Grade A)
- Additional strategies to prevent OHSS which may be helpful include the use of metformin in PCOS patients (Grade A), aspirin administration (Grade A), and cryopreservation of embryos. (Grade B)
- The mainstay of OHSS treatment includes fluid resuscitation and prophylactic anticoagulation.
- Paracentesis or culdocentesis may be recommended for management of OHSS when a large amount of ascites is present. (Grade B)

Definitions

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Strength of Recommendations

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Ovarian hyperstimulation syndrome (OHSS)

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Endocrinology

Obstetrics and Gynecology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To identify who is at high risk, how to prevent ovarian hyperstimulation syndrome (OHSS), and the treatment for existing OHSS

Target Population

Female patients undergoing controlled ovarian stimulation with gonadotropins during assisted reproduction

Interventions and Practices Considered

Risk Assessment

- Demographic factors (age, body mass index, race, infertility diagnosis, presence or absence of polycystic ovary syndrome [PCOS])
- Ovarian reserve markers (antral follicle count, antimüllerian hormone [AMH] levels, inhibin A/B levels)
- Ovarian stimulation parameters (follicles, oocytes, estradiol)

Prevention

- Type of stimulation protocol (gonadotropin-releasing hormone [GnRH] antagonist versus GnRH agonist)
- Aspirin
- Metformin
- Choice of trigger for final oocyte maturation prior to retrieval
- Dopamine agonist (cabergoline)
- Calcium
- Cryopreservation of embryos

Treatment

- Paracentesis or culdocenteses

Note: The following were considered but there was insufficient evidence to make a recommendation for prevention of ovarian hyperstimulation syndrome (OHSS): clomiphene, coasting, lower dose of human chorionic gonadotropin (hCG), albumin, luteal antagonist administration, letrozole, methylprednisolone, intramuscular progesterone, or ketoconazole. Volume expanders were considered for treatment but there was insufficient evidence to make a recommendation.

Major Outcomes Considered

- Risk of ovarian hyperstimulation syndrome (OHSS) (serum estradiol concentrations, serum antimüllerian hormone [AMH] levels, antral follicle count [AFC])
- Incidence of OHSS
- Pregnancy, implantation, and live birth rates
- Duration of hospitalization

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A systematic review of the literature was performed in the electronic database MEDLINE through PubMed, with a filter for human subject and English research, on September 10, 2015.

A combination of the following medical subject headings or text words were used: acetylsalicylic acid, age, albumin, ASA, ascites, aspirin, BMI, body mass index, calcium, clinical trial, clomiphene, enoxaparin, freeze, freeze-all, heparin, "last 5 years," Lovenox, obes*, metformin, OHSS, ovarian hyperstimulation syndrome, paracentesis, prevention, prednisolone, prednisone, risk factors, *stimulation, treatment (limited to "clinical trial"), and weight*.

Initially, titles and abstracts of potentially relevant articles were screened and reviewed for inclusion/exclusion criteria. Protocols and results of the studies were examined according to specific inclusion criteria. Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy, implantation, or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles.

Summary of the Inclusion/Exclusion Criteria

Include	**Exclude**
Level 1, 2-1, 2-2 studies	Level 3 studies: series, case reports, reviews, opinions, off topic
Level 2-3 studies only for question 3 (due to paucity of available data)	Level 2-3 (questions 1 and 2)
Human studies	Animal studies
English	Non-English
Studies with a comparison group	Studies without a comparison group
In vitro fertilization (IVF) studies	Non-IVF studies; intrauterine insemination (IUI) studies; in vitro maturation (IVM) studies
≥10 ovarian OHSS events (observational); any OHSS events (randomized controlled trials [RCTs])	<10 OHSS events (observational)
Studies that address clinical risk factors	Studies that address only serum markers
Studies that assess antimüllerian hormone (AMH) as a marker	Studies that focus on type of gonadotropin used
	Studies that assess glucocorticoids

Four members of an independent task force reviewed the full articles of all citations that possibly matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and solved by consensus or arbitration after consultation with an independent reviewer/epidemiologist.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

Number of Source Documents

The electronic search and examination of reference lists from primary and review articles yielded 1,245 studies, of which 144 studies were included.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The quality of the evidence was evaluated using the grading system found in the "Rating Scheme for the Strength of the Evidence" field and is assigned for each reference in the bibliography (see the original guideline document).

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The literature was reviewed to answer the following questions:

Who is at high risk for ovarian hyperstimulation syndrome (OHSS)?
How can we prevent OHSS?
Treatment for OHSS?

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document was reviewed by American Society for Reproductive Medicine members, and their input was considered in the preparation of the final document. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Identifying women who are at high risk of ovarian hyperstimulation syndrome (OHSS) is essential to lowering, and potentially eliminating, the incidence of OHSS.

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Foreign Language Translations

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Dec

Guideline Developer(s)

American Society for Reproductive Medicine - Nonprofit Organization

Source(s) of Funding

American Society for Reproductive Medicine

Guideline Committee

Practice Committee of the American Society for Reproductive Medicine

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Financial Disclosures/Conflicts of Interest

All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the American Society for Reproductive Medicine Web site .

Availability of Companion Documents

Continuing medical education (CME) credit related to this guideline is available from the American Society for Reproductive Medicine Web site .

Patient Resources

The following is available:

> Ovarian hyperstimulation syndrome (OHSS). Fact sheet. Birmingham (AL): American Society for Reproductive Medicine; 2014. 1 p. Available from the ReproductiveFacts Web site . Also available in Spanish from the ReproductiveFacts Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on March 27, 2017. The information was verified by the guideline developer on April 17, 2017.

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